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POST-AUTHORISATION SAFETY COHORT OBSERVATION OF RETACRIT (epoetin zeta) ADMINISTERED SUBCUTANEOUSLY FOR THE TREATMENT OF RENAL ANAEMIA (PASCO II)

OBSERVATION PROTOCOL

Final Protocol Date:	**30 March 2010, Protocol Version 1.0**
Amendment 1 Date:	**05 August 2010, Protocol Version 2.0**
Amendment 2 Date:	05 March 2012, Protocol Version 3.0
Amendment 3 Date:	20 March 2015, Protocol Version 4.0
Amendment 4 Date:	**02 August 2019, Protocol Version 5.0**
Project number	**EPOE-09-11**

GLOBAL PROTOCOL AMENDMENT 4: SUMMARY OF CHANGES

The purpose of this protocol amendment is to implement the following changes to the study protocol:

- To document the change of bioanalytical laboratory and technical assay for anti-drug antibody (ADA)/neutralising antibody (NAb) analysis.

- To document the plan, following consultation with the EMA, to reduce the planned total sample size for the study in line with the observed incidence rate of Pure Red Cell Aplasia (PRCA). Enrolment in the STADA study will now end; and the observation of ongoing patients will end in April 2020, when the last patient enrolled by Hospira is due to complete the 3-year observation.

  This will enable the Hospira & STADA patient data to be combined, resulting in a total sample size of at least 6206 patients and the combined data will be reported to the EMA in a joint clinical study report.

- To incorporate standard safety reporting language from the current Pfizer non-interventional study (NIS) protocol template.

In addition, this amendment also incorporates into the protocol the following non-substantial/administrative changes which have been previously documented via Protocol Administrative Change Letter (PACL):

- PACL dated 22 November 2016.
  - Change to adverse drug reaction (ADR)/adverse event of special interest (AESI) reporting contact details and to ADR/AESI Report Forms following Pfizer acquisition of Hospira.

- PACL dated 16 May 2018.
  - Extension of maximum observation period for PASCO II from 8 years to 12 years to reflect the extended period of study recruitment which was necessary to recruit the required number of patients for the study.
  - Change of name for IPM laboratories to BioAgilytix Europe GmbH.
  - Clarification of 'Legal Representative' definition for Informed Consent.

- PACL dated 21 November 2018.
  - Transfer of Marketing Authorisation (MAH) Holder from Hospira UK Limited to Pfizer Europe MA European Interest Grouping (EEIG) (PACL, dated 21 Nov 2018).
  - Abbreviation updates.

These PACLs are provided for further information in Appendix 1. See 'Summary of Changes in Amended Non-Interventional Study (NIS) Protocol - Global Protocol Amendment 4' for an itemized list of all text changes made from Protocol v4.0 (20 March 2015) to Protocol v5.0 (02 August 2019) with section references.

The following table summarises the protocol amendment updates made to date for this study:

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
4	02 August 2019	Section 7.8.1	Change of bioanalytical laboratory and technical assay for ADA/NAb analysis. To document the reduction of planned sample size. To incorporate standard Pfizer safety reporting language from the current Pfizer non-interventional study (NIS) protocol template.	Previous laboratory no longer supported the technical assay used for the study. To document the plan, following consultation with the EMA, to reduce the planned total sample size for the study in line with the observed incidence rate of Pure Red Cell Aplasia (PRCA). Enrolment in the STADA study will now end; and the observation of ongoing patients will end in April 2020, when the last patient enrolled by Hospira is due to complete the 3-year observation. This will enable the Hospira & STADA patient data to be combined, resulting in a total sample size of at least 6206 patients and the combined data will be reported to the EMA in a joint clinical study report. Pfizer standard safety language is incorporated to ensure consistency with current Pfizer processes.
3	20 March 2015	Abstract, Section 5, Section 6, Section 8, Section 9, Section 14	Addition of requirement to report occurrences of overdose and treatment error in order to comply with current guidance. Changes to sections relevant to safety reporting and guidance in order to be consistent with current guidances and practice. Removal of the Retacrit summary of product characteristics (SmPC) as an appendix. in order to avoid unnecessary protocol	To remain consistent with current guidances and practices. To remove the SmPC as an appendix in order to avoid unnecessary protocol amendments, if the SmPC is updated, in the future. To provide clarity regarding the eligibility criteria.

			amendments, if the SmPC is updated, in the future. Clarification of wording of selection criteria regarding expected availability of patients for observation for 3 years.	
2	05 March 2012	Section 8.8.1, Section 8.9.3	To provide clarification on the safety reporting form/s to be used for reporting AESI.	AESI to be documented on appropriate targeted AESI report forms.
1	05 August 2010	Abstract, Section 8.5, Section 8.7	Removal of reference to specific SmPC version in protocol text.	To remove the need to update the protocol each time the SmPC is updated.

1. ABSTRACT AND FLOW CHART

1.1. Abstract

NAME OF SPONSOR: Hospira UK Limited	NAME OF FINISHED PRODUCT: Retacrit	NAME OF ACTIVE INGREDIENTS: Epoetin zeta
TITLE	Post-Authorisation Safety Cohort Observation of Retacrit (epoetin zeta) Administered Subcutaneously for the Treatment of Renal Anaemia (PASCO II).	
PRIMARY OBJECTIVE	To estimate the incidence of Pure Red Cell Aplasia (PRCA), neutralising antibodies, lack of efficacy, and thromboembolic events under treatment with Retacrit (epoetin zeta) administered subcutaneously (SC) in patients with renal anaemia.	
SECONDARY OBJECTIVE	To obtain information on adverse drug reactions (ADR) associated with Retacrit (epoetin zeta), use of epoetin zeta during pregnancy and lactation and data on long term use.	
OBSERVATION DESIGN	Non-interventional, longitudinal, multi-centre, defined population, prospective observation.	
PLANNED SAMPLE SIZE	6700 patients planned. Study will now end with at least 6206 patients enrolled.	
OBSERVATION CENTRES	Centres treating patients with renal disease and dialysis centres.	
PATIENT SELECTION CRITERIA	Patients are eligible for enrolment if the following applies: • Patients currently under treatment with Retacrit (epoetin zeta) administered SC for renal anaemia; • Informed consent given in writing after being provided with detailed information about the characteristics of this observation by the physician; • Patients expected to be available for 3 years of observation; Patients are <u>not eligible</u> for enrolment if the following applies: • Any contraindications as per the current SmPC of Retacrit.	
FORMULATION	According to the current SmPC of Retacrit	

NAME OF SPONSOR: Hospira UK Limited	NAME OF FINISHED PRODUCT: Retacrit	NAME OF ACTIVE INGREDIENTS: Epoetin zeta
DOSAGE	Dosage as medically required for the treatment of the individual patient as determined by the patients' healthcare professional.	
ROUTE OF ADMINISTRATION	Only patients who are currently under SC treatment should be included in the observation.	
DURATION OF OBSERVATION	Planned that up to 3 years observation for each patient will be documented. Observation of ongoing patients will now end in April 2020.	
PRIMARY ENDPOINTS	Incidence rate of adverse events of special interest: • Pure red cell aplasia; • Neutralising antibodies; • Lack of efficacy; • Thromboembolic events including cerebrovascular events (eg, cerebrovascular accident, cerebral infarction, cerebral haemorrhage, transient ischaemic attack), deep vein thrombosis, myocardial infarction, and pulmonary embolism.	
SECONDARY ENDPOINTS	Descriptive evaluation including incidence rates of ADRs, pregnancy/lactation exposure and long-term use	

NAME OF SPONSOR: Hospira UK Limited	NAME OF FINISHED PRODUCT: Retacrit	NAME OF ACTIVE INGREDIENTS: Epoetin zeta
PROCEDURE	This is a non-interventional, multi-centre, longitudinal observation with a defined population using a prospective cohort design. All steps related to the selection and enrolment of patients and the treatment of these patients will be in accordance with standard medical care. The decision to treat a patient will be independent of the decision to enrol a patient. All participating physicians will be asked if blood samples obtained from routine laboratory determinations **before** start of treatment with Retacrit (pre-dose serum sample) are available. Such samples would be centrally stored and, if necessary, analysed in a specialised laboratory for determination of neutralising antibodies. The following information will be collected per patient: • Pseudonymised patient identification; • Demographic data; • Medical history including selected risk factors; • Exposure to erythropoiesis-stimulating agents (ESA); • Start of treatment with Retacrit; • Adverse drug reactions; • Adverse events of special interest; • Pregnancy and lactation periods, if applicable.	
STATISTICAL ANALYSIS	The incidence rate of adverse events of special interest will be calculated per patient. The ADRs will be evaluated and described including incidence rates.	

1.2. Flow Chart

Type of assessment planned	Entry examination	ongoing	Final examination
	Day 0		Week 156
Patient selection criteria	**X**	--	--
Informed consent	**X**	--	--
Pseudonymised patient identification	**X**	--	--
Demography	**X**	--	--
Exposure to ESA	**X**	--	--
Medical history	**X**	--	--
Retaining of blood samples for determination of neutralising antibodies	**X***	**X****	**X***
Occurrence of pregnancy/lactation	**X**	**X**	**X**
Adverse drug reactions	--	**X**	**X**
Adverse events of special interest (primary endpoints)	--	X	X

* if available.
** if formation of antibodies is suspected or on request by the physician.

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3. LIST OF ABBREVIATIONS AND TERMS

ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
CHMP	Committee for Medicinal Products for Human Use
CRF	Case Report Form
CRO	Contract Research Organisation
DSU	Drug Safety Unit
ECL	Electrochemiluminescence
EDC	Electronic Data Capture
EDP	Exposure During Pregnancy
EEIG	European Economic Interest Groupings
EMA	European Medicines Agency
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agents
GVP	Good Pharmacovigilance Practice(s)
HLT	High level term
HLGT	High Level Group Term (HLGT)
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralising antibody(ies)
NIS	Non-Interventional Study

PACL	Protocol Administrative Change Letter
PRAC	Pharmacovigilance Risk Assessment Committee
PRCA	Pure red cell aplasia
PSUR	Periodic Safety Update Report
PT	Preferred term
rh-EPO	Recombinant human erythropoietin
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard Operating Procedure

4. ETHICAL AND LEGAL ASPECTS

This observation will be conducted in accordance with the following regulatory documents:

- Guideline on Good Pharmacovigilance Practices (GVP): Module VIII – Post Authorisation Safety Studies;
- Directive 2001/83/EC, as amended, of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use;
- Applicable national legislation;
- Standard Operating Procedure (SOP) system of the sponsor;
- Applicable Contract Research Organisation (CRO) SOPs.

4.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

As required by GVP Module VIII on Post-Authorisation Safety Studies the study protocol will be submitted for review and approval by the relevant Institutional Review Board/Independent Ethics Committee.

4.2. Notification

For notification procedures to regulatory authorities or other bodies the applicable national legislation should be followed.

4.3. Patient Information/Informed Consent

Regarding the decision about therapy, there is no further information necessary which is beyond the physician's routine professional duty to inform the patient.

In this non-interventional study the physician is asked to provide, if available, remaining serum/plasma samples gained from routine laboratory determinations to a central specialised laboratory for the evaluation of the presence of anti-epoetin antibodies. In this case it is necessary to inform patients (and their witness, where appropriate), or in the case of minors, patients and their legal representatives of these potential additional lab tests and obtain written informed consent for the testing.

Participating patients (and their witness, where appropriate) or, in the case of minors, patients and their legal representatives will be informed and asked for written informed consent regarding the collection and evaluation of data during the course of the non-interventional study.

The physician will ensure by written confirmation that informed consent was obtained and is available. The written confirmation and the informed consent will be archived by the physician.

5. INTRODUCTION

Erythropoietin is an essential growth factor required for production of red blood cells. The stimulus for erythropoietin production is believed to be the oxygen content of blood delivered to the renal interstitial cells. When the peritubular renal cells are functioning correctly, individuals with low haemoglobin concentrations will produce increased quantities of erythropoietin, resulting in increased red blood cell production (Ridley et al., 1994; Wang and Semenza, 1996; Lacombe and Mayeux, 1999).[6,8,4]

Chronic renal failure is characterised by a progressive loss of kidney function resulting from inherited disorders or conditions such as diabetes mellitus or hypertension. In patients with chronic renal failure, deficiency of erythropoietin production is the primary cause of anaemia.

Information on indication, posology, contraindication, interaction and side effects of Retacrit are specified in the current SmPC of Retacrit.

6. OBSERVATION OBJECTIVE

The primary objective of the observation is to estimate the incidence of Pure Red Cell Aplasia (PRCA), neutralising antibodies, lack of efficacy and thromboembolic events under treatment with Retacrit (epoetin zeta) administered SC in patients with renal anaemia.

The secondary objective is to obtain information on ADR associated with Retacrit (epoetin zeta), use of epoetin zeta during pregnancy and lactation and data on long term use.

7. OBSERVATION PLAN

7.1. Overall Observation Design

The most important points regarding the planned design are the following:

- Non-interventional;
- Longitudinal;
- Multi-centre;
- Defined population;
- Prospective cohort observation;
- Subcutaneous administration;
- 6700 patients with renal anaemia;
- Duration of observation: up to 3 years per patient.

The observation will take place at centres treating patients with renal disease and dialysis centres.

The study will now end with at least 6206 patients enrolled; and the observation of ongoing patients will end in April 2020, when the last patient enrolled by Hospira is due to complete the 3-year observation.

7.2. Discussion of the Observation Design

Epoetin-associated PRCA is characterised by severe anaemia, low reticulocyte count, absence of erythroblasts, neutralising antibodies against erythropoietin and as a consequence nonresponse to therapeutically administered epoetin. Between 1999 and 2004, a total of 191 patients with epoetin-associated PRCA were identified in Australia, Canada, and certain countries of Europe and Asia, 95 percent of which were observed among haemodialysis patients who received several months SC a particular formulation of epoetin alfa that contained polysorbate 80 as stabiliser. Experience with the increase of PRCA between 1999 and 2004 identified SC use as risk factor and patients with renal anaemia as population at risk. Exposure-adjusted incidence rates peaked in 2002 at 4.5 per 10000 patient years (McKoy et al., 2008).[5]

Changes of the formulation of that specific product as well as pharmacovigilance efforts and safety guidance resulted in a greater than 95 percent decrease in the number of new cases of epoetin-associated PRCA. Since then antibody-mediated PRCA is regarded as a rare class-related toxicity that occurs after extended periods of SC administration of epoetins to chronic renal failure patients with an incidence rate of 0.02 to 0.03 per 10000 patient years (McKoy et al., 2008).[5]

The present post authorisation non-interventional observation, which is part of the marketing authorisation holder's (MAH) post-approval commitment for further pharmacovigilance surveillance, is planned as a prospective cohort study enrolling patients with renal anaemia treated SC with epoetin zeta under routine conditions in a widespread use. It was initially planned that a prospective cohort of 6700 patients would be followed up to 3 years treatment per patient with epoetin zeta.

The sample size was chosen accordingly to detect cases of epoetin-associated PRCA in order to demonstrate that the incidence rate under treatment with epoetin zeta is substantially below the risk observed between 1999 and 2004 and that it can be reasonably concluded that the incidence is in the range of the incidence of the class of ESA.

Although powered primarily to verify that no immunogenicity concern arises from the SC use of epoetin zeta, this observation will also be helpful due to its large sample size in providing further information about the incidence of thromboembolic events in patients with renal anaemia treated with ESAs.

Following consultation with the EMA, it is now planned to reduce the total sample size for the study in line with the observed incidence rate of PRCA, to at least 6206 patients (see Section 10.3 for more details).

7.3. Time Schedule

The overall time schedule for the observation was initially planned as follows:

- Start of observation: 2010;
- Observation period per patient: up to 3 years;
- Observation period PASCO II max. 12 years;
- End of observation: 6700 patients completed the observation;
- Final report: end of observation + 11 months.

Safety interim data will be compiled and reported in the framework of periodic safety update report (PSUR) and risk management plan (RMP) submissions. Annual progress reports submitted to Pharmacovigilance Risk Assessment Committee (PRAC) as per GVP Module VIII.

The study will now end with at least 6206 patients enrolled; and the observation of ongoing patients will end in April 2020, when the last patient enrolled by Hospira is due to complete the 3-year observation.

7.4. Participation of Healthcare Professionals

The decision to treat patients with Retacrit will be independent of the decision to enrol patients into the observation cohort. According to GVP Module VIII B.3 subject to the healthcare professional's terms of service, payment is restricted to compensation of the healthcare professional for any additional time and expenses incurred. No additional payment or inducement for a healthcare professional to participate in this post-authorisation safety observation is offered or given.

In order to avoid selection bias physicians participating in this observational cohort study should include patients, who are started on treatment with Retacrit and are willing to participate, consecutively.

7.5. Patient Selection Criteria

Patients are eligible for enrolment if the following applies:

- Patients treated SC with Retacrit (epoetin zeta) for renal anaemia.
- Informed consent given in writing after being provided with detailed information about the characteristics of this observation by the physician.
- Patients expected to be available for 3 years of observation.[1]

[1] IMPORTANT NOTE: Data must only be collected from patients in person; not via 3rd parties.

Patients are not eligible for enrolment if the following applies:

- Any contraindication as per the current SmPC of Retacrit.

7.6. Premature Discontinuation

Patients may withdraw at their own request without providing any reason. Decisions on treatment discontinuation or changes will be solely based on medical reasons, which are in the best interest of the patients. These decisions will be made independent of considerations of continuation in the observation. Patients who are discontinued from Retacrit treatment because of adverse events of special interest, or ADR, or pregnancy should be followed up until their medical condition is resolved or stabilised.

7.7. Treatment

7.7.1. Identity of Medication

1. Name of product: Retacrit
2. Active ingredient: epoetin zeta
3. Mode of administration: subcutaneous
4. Prescription status: only available on prescription
5. Marketing authorisation holder: Pfizer Europe MA EEIG

For further information see current SmPC of Retacrit.

7.7.2. Posology and Mode of Administration

Dosage as medically required for the treatment of the individual patient as determined by the patients' healthcare professional.

The initial Retacrit dosage will be documented in the Case Report Form (CRF) as total dosage per week and frequency of dose per week.

7.7.3. Duration of Treatment

The decision about the duration of treatment with Retacrit lies with the physician and is independent of his participation in this cohort observation. Within PASCO II the observation of treatment was planned to be up to 3 years per patient. However, observation of ongoing patients will now end in April 2020, when the last patient enrolled by Hospira is due to complete the 3 year observation.

7.7.4. Overdose and Medication Error

Any occurrence of overdose or medication error occurring during the study should be reported to Pfizer Drug Safety Unit (DSU), using the Pfizer Adverse Event (AE) Report form.

Overdose is defined as administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgment should always be applied.

Medication error is defined as an unintentional error in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer.

7.8. Safety Criteria

Primary endpoints:

Incidence rate of adverse events of special interest:

- Pure red cell aplasia;
- Neutralising antibodies;
- Lack of efficacy (as defined in the current SmPC);
- Thromboembolic events including cerebrovascular events (eg, cerebrovascular accident, cerebral infarction, cerebral haemorrhage, transient ischaemic attack), deep vein thrombosis, myocardial infarction, and pulmonary embolism observed under treatment with Retacrit (epoetin zeta) administered SC in patients with renal anaemia.

Secondary endpoints:

Descriptive evaluation including incidence rates of ADRs.

Information on treatment with Retacrit (epoetin zeta):

- During pregnancy and lactation;
- On long term use.

7.8.1. Methods of Assessment of Data

All patient data assessed will be pseudonymised before transferred to the sponsor.

7.8.1.1. Primary Endpoints

Documentation of adverse events of special interest (AESI)

AESI will be documented in the CRF and on a continuous basis on the Pfizer AE Report Form.

Reporting is independent of a causal relationship.

The following key information will be documented on the Pfizer AE form:

- Diagnosis or main symptom;
- Description of the course of the event;
- Diagnostic test results to confirm diagnosis;
- Pre-existing risk factors for development of the event and other relevant medical history;
- Start date, end date or continuation of the event;
- Outcome of the event;
- Therapy of event;
- Event seriousness;
- Start date of Retacrit treatment, total weekly dose and date of last administration before event onset;
- Causal relationship between Retacrit and the event;
- Action taken with Retacrit;
- Performance of Retacrit re-administration and in case of re-administration recurrence of event;
- Concomitant medication;
- In case of fatal or life-threatening events: autopsy reports and/or hospital letters.

For more detailed definition of AEs and description of the additional documentation and reporting procedures see Section 10.

Anti-epoetin antibodies

In suspicious cases with respective clinical symptoms for PRCA, the sponsor has to be informed immediately (contact data see Section 8.) and the blood samples of the respective patients will be analysed. Blood samples to be analysed will include, if available, blood samples (serum sample of at least 2 ml) from routine determinations taken:

- Before the start of treatment with Retacrit (pre-dose);
- During PRCA clinical symptoms;
- And, from the patient's final examination visit.

The analysis of binding antidrug antibodies (ADA) against recombinant human erythropoietin (rh-EPO) in human serum samples is performed by a bridging Electrochemiluminescence (ECL) assay. Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. The sample analysis will follow a tiered approach of screening, confirmation, and titer determination.

The bioanalytical laboratory for the evaluation of antibodies will be:

QPS LLC
Delaware Technology Park
1 Innovation Way Suite 200
Newark, DE 19711
USA
Tel +1 (302) 369-5601
Fax +1 (302) 7373759

Blood samples will be shipped from study sites to the following laboratory for storage. Blood samples will be shipped from here to the QPS bioanalytical laboratory, if analysis is required:

BioAgilytix Europe GmbH
Lademannbogen 10
22339 Hamburg, Germany
Phone: +49 (0) 40 5267791
Email: pasco@bioagilytix.de

Depending on the results of the ADA assay and the clinical symptoms of the patient, further investigations, eg, the neutralising capacity of the antibodies (NAb), can be initiated.

7.8.1.2. Secondary Endpoints

Documentation of ADRs

Adverse drug reactions will be documented in the CRF and on a continuous basis on the Pfizer AE Report Form. For more detailed definition of ADRs see Section 8.2. ADRs will be fully documented on the Pfizer AE Report Form including the following key information:

- Diagnosis or main symptom;
- Description of the course of the reaction, if needed;
- Start date, end date or continuation of the reaction;
- Outcome of the reaction;
- Therapy of reaction;
- Reaction seriousness;

- Start date of Retacrit treatment, total weekly dose and date of last administration before reaction onset;
- Causal relationship between Retacrit and ADR;
- Action taken with Retacrit;
- Performance of Retacrit re-administration and in case of re-administration recurrence of reaction;
- Concomitant medication and medical history;
- In case of fatal or life-threatening events: autopsy reports and/or hospital letters.

Documentation of Retacrit exposure during pregnancy and lactation

Retacrit exposure during pregnancy and lactation will be documented in the CRF and on a continuous basis on the Pfizer AE Report Form, as well as Exposure During Pregnancy (EDP) supplemental form. Refer to reporting procedure in Section 8. Retacrit induced ADR occurrence of the suckling during lactation will be followed up by routine pharmacovigilance. Pregnancies will be followed up until a final outcome is known. Live off-spring will be followed for at least 8 weeks after delivery.

7.8.1.3. Additional Data

Demographic data

At entry examination the physician documents the following data in the CRF:

- Pseudonymised patient identification (patient number);
- Date of birth;
- Ethnic origin;
- Gender;
- Height;
- Dry weight (weight measured post-dialysis in indoor clothing without shoes);
- First assessment of haemoglobin, haematocrit and vital signs (systolic and diastolic blood pressure and heart rate) in the week of the entry examination;
- Availability of signed informed consent.

Medical history: selected risk factors

At entry examination the following information will be documented in the CRF by tick boxes:

- Coronary heart disease;
- Myocardial infarction;
- Atrial fibrillation;
- Other arterial or venous thrombotic or embolic events;
- Peripheral arterial disease;
- Cerebrovascular disease;
- Transient cerebral ischaemic attack;
- Stroke;
- Thrombosis of deep vessels of lower extremities;
- Pulmonary embolism;
- Hyperlipidaemia;
- Hypertension;
- Diabetes (type 1/type 2, diabetic vascular complications yes/no);
- Heart failure (NYHA stage);
- Cancer (type of cancer, Date: since when);
- Smoking (current smoker, ex-smoker, never-smoker).

Medical history: other

At entry examination the following information will be documented in the CRF:

- Diagnosis leading to renal failure;
- Date of first diagnosis of renal failure;
- Other relevant medical history;
- Date of first dialysis, average frequency of dialysis;

- Date of first treatment with any ESA and average dose for the last 3 months.

Retacrit treatment

Following information will be documented in the CRF:

- First Retacrit treatment;
- Retacrit dosage as total dosage per week and frequency of dosage per week in the week of the entry examination;
- Route of administration;
- Retacrit holidays.

Premature termination

The reason for premature discontinuation of PASCO II participation will be documented in the CRF.

8. ASSESSMENT OF SAFETY

8.1. REQUIREMENTS

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Pfizer AE Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) adverse events of special interest (AESIs); (2) adverse drug reactions (ADRs); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "DEFINITIONS OF SAFETY EVENTS."

Table 8.1. Safety Reporting Requirements

Safety event	Recorded on the case report form	Reported on the AE Report Form to Pfizer Safety within 24 hours of awareness
AESIs (non-serious and serious)	All	All
ADRs (non-serious and serious)	All	All
Additional scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AESI/ADR) Note: Any associated AESI/ADR is reported together with the exposure scenario.

For each safety event, the investigator must pursue and obtain information adequate both to determine the outcome of the safety event and to assess whether it meets the criteria for classification as serious (refer to "Serious AESI" and "Serious Adverse Reaction" sections below).

All safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to** Retacrit. In particular, if the safety event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the case report form. In general, this will include a description of the safety event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.1.1. Reporting Period

For each patient, the safety event reporting period begins at the time of the patient's first dose of Retacrit or the time of the patient's informed consent if s/he is being treated with Retacrit at study start, and lasts through the end of the observation period of the study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. Most often, the date of informed consent is the same as the date of enrolment. In some situations, there may be a lag between the dates of informed consent and enrolment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enrol the patient.

8.1.2. Causality Assessment

The investigator is required to assess and record the causal relationship. For all safety events, sufficient information should be obtained by the investigator to determine the causality of each safety event. For safety events with a causal relationship to Retacrit, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that Retacrit caused or contributed to a safety event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether Retacrit caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that Retacrit did not cause the event, this should be clearly documented on the AE Report Form.

8.2. DEFINITIONS OF SAFETY EVENTS

Adverse Events of Special Interest (AESIs)

AESIs are adverse medical occurrences, which have been determined by the sponsor as being important for the safety evaluation of Retacrit. Adverse events of special interest are documented and recorded from the time when the patient has signed the informed consent until the end of the observation period, independently of causality assessments. For the purpose of this non-interventional study the following medical diagnoses fall under the definition of an adverse event of special interest:

- Pure red cell aplasia;
- Neutralising antibodies;
- Lack of efficacy;
- Thromboembolic events including cerebrovascular events (eg, cerebrovascular accident, cerebral infarction, cerebral haemorrhage, transient ischaemic attack), deep vein thrombosis, myocardial infarction, and pulmonary embolism.

Serious AESI

An AESI which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether an event should be considered a serious AESI, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. An example of such an event may be a trans ischemic attack that may not fall into any of the 5 serious criteria but could be considered by the investigator as a medically important based on his/her medical judgement.

Adverse Drug Reaction (ADR)

An adverse drug reaction is a response to a medicinal product which is noxious and unintended. (Good Pharmacovigilance Practice Annex I - Definitions).

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

Unexpected adverse reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the SmPC.

This includes class-related reactions which are mentioned in the SmPC but which are not specifically described as occurring with this product. For products authorised nationally, the relevant SmPC is that authorised by the competent authority in the Member State to whom the reaction is being reported.

For centrally authorised products, the relevant SmPC is the SmPC authorised by the European Commission. During the time period between a Committee for Medicinal Products for Human Use (CHMP) opinion in favour of granting a marketing authorisation and the Commission decision granting the marketing authorisation, the relevant SmPC is the SmPC annexed to the CHMP opinion.

(Good Pharmacovigilance Practice Annex I - Definitions).

Serious adverse reaction

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe. Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

(Good Pharmacovigilance Practice Annex I - Definitions).

Other Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) Retacrit, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to Retacrit (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to Retacrit prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated safety event.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with Retacrit, this information must be submitted to Pfizer, irrespective of whether a safety event has occurred using the AE Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to Retacrit in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the AE Report Form and the EDP Supplemental Form. This must be done irrespective of whether a safety event has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated safety event.

Medication error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labelling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated safety event:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by a safety event.

- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
    - An identifiable reporter;
    - A suspect product;
    - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated safety event.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated safety event.

9. DATA QUALITY ASSURANCE

9.1. Monitoring

Checks for plausibility and completeness will be performed automatically while entering data in the Electronic Data Capture (EDC) system. Relevant missing information and discrepancies will be followed by queries.

The conduct of this observational cohort study will be supervised by designated monitors. A monitoring plan will describe scope, objective, responsibilities and procedures of monitoring.

Data checks will include:

- Confirmation of informed consent;
- Documented AEs of special interest (primary endpoints);
- Documented ADRs;
- Documented cases of pregnancy/lactation;
- Confirmation that the patient is receiving SC Retacrit;
- Documentation of serum samples and shipments (if applicable).

9.2. Data Handling

Data will be entered directly by the centres into the EDC systemvia electronic CRFs. An approval of the data by electronic signature is mandatory. During data entry, plausibility checks will be performed. If required paper CRFs will be made available for centres that do not have the capability of EDC. The data will be statistically evaluated and will be narrated in a final report.

Data handling will be performed according to national data protection laws.

10. BIOMETRICS AND STATISTICAL ASPECTS

10.1. General Approach

All analyses will be specified in detail in a Statistical Analysis Plan (SAP). All data will be described appropriately.

10.2. Safety Analysis

The primary endpoints in this cohort observation are PRCA, neutralising antibodies, lack of efficacy and thromboembolic events including cerebrovascular events (eg cerebrovascular accident, cerebral infarction, cerebral haemorrhage, transient ischaemic attack), deep vein thrombosis, myocardial infarction, and pulmonary embolism (documentation of adverse events of special interest; see Section 8). Adverse drug reactions, pregnancy/lactation and long-term use are secondary endpoints.

In general, it is recognised that most of the untoward medical occurrences (unfavourable and unintended signs, symptoms, or diseases) occurring in patients with renal failure can be explained by the poor underlying condition of the patients; most of these events are independent of the administration of epoetin zeta. There is often an under-reporting of these events, especially in case of no (double-blind) control treatment. In order to increase the quality of the recording and documentation of events potentially affected by epoetin zeta this project will focus on the recording of ADRs.

Patients can experience more than one ADR and the same ADR can occur more than once in the same patient. A single ADR report form may contain several events with the same ADR onset date. Multiple ADRs in the same patient are medically and consequently statistically dependent. Therefore, ADR rates should be calculated on patient counts.

The (crude) incidence rate is defined as the number of patients who experience a certain event (eg a specific Medical Dictionary for Regulatory Activities [MedDRA] Preferred Term), divided by the number of patients at risk. For the purpose of this cohort observation, a patient at risk is a patient who was exposed to epoetin zeta (ie, epoetin zeta was applied at least once) after enrolment into PASCO II. The incidence rate will also be evaluated using the number of patient years exposed to epoetin zeta as the denominator.

The incidence rate is appropriate to describe the risk of an ADR if patients are observed for approximately the same period of time. Nevertheless, for a treatment and observation period of about three years the time pattern of occurrence is also of importance and the interpretation of the ADR profile should not be based on overall incidences only. At least for

MedDRA Preferred Terms with an overall incidence of 0.05 or more the exact time pattern will therefore be displayed by cumulative ADR incidences derived from life-table analysis for 2-monthly intervals. The cumulative incidence accounts for the actual duration of follow-up as well as the time pattern of when the time pattern of when the events occur relative to the number of patients at risk.

ADR incidences will be displayed by MedDRA primary System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT) and Preferred Term (PT).

In addition, 95% confidence limits will be calculated. If the number of ADR on the MedDRA PT level is 0 or 1, the 95% confidence intervals for crude rates will be derived from the continuity-corrected "score interval method" [Vollset, S.E. (1993): Confidence Intervals for a Binomial Proportion. Statistics in Medicine 12, 809 - 824] using the approach of Blyth and Still [Binomial Confidence Intervals. Journal of the American Statistical Association, 78, 108 - 116]. Confidence intervals for the cumulative adverse event incidence will be based on Greenwood's formula [Kalbfleisch, JD., Prentice, RL. (1980):[3] The Statistical Analysis of Failure Time Data. John Wiley and Sons. New York]. It must be taken into account that the confidence limits have to be interpreted in an exploratory sense, not as exact statistical error probabilities.

The analyses will be restricted to those patients who receive epoetin zeta at least in part within PASCO II.

10.3. Sample Size Considerations

As outlined in Section 7.2 the exposure-adjusted incidence of PRCA due to neutralising antibodies had a peak in 2002, with 4.5 per 10000 patient years; this corresponds to an incidence of 0.045% per patient year. Meanwhile antibody-mediated PRCA is regarded as a rare class-related toxicity that occurs after extended periods of SC administration of ESA to chronic renal failure patients, with an incidence of 0.02 to 0.03 per 10000 patient years; this corresponds to an incidence of 0.0002% to 0.0003% per patient year.

A prospective cohort will be followed up to 3 years treatment per patient with epoetin zeta. Alternatively, one might consider observing more patients over a shorter period of time (eg, 1 year) or fewer patients for even a longer period. The selected approach is regarded as a good compromise which takes into account that on the one hand increases over time and that the number of available patients might be limited, and on the other hand also allows generating sufficient data within a reasonable period.

The sample size was chosen to detect cases of epoetin-associated PRCA in order to the incidence rate under treatment with epoetin zeta is substantially below the incidence of 4.5 per 10000 patient years (this corresponds to an incidence of 0.135% within 3 years) observed in 2002.

As the recruitment rate of the STADA part of the study was considerably lower than expected, it was not possible to enrol the planned number of patients within the anticipated timeframe.

Therefore, following consultation with the EMA, the planned total sample size for the study will be reduced in line with the observed incidence rate of PRCA. Accordingly, enrolment in the STADA study will now end; and the observation of ongoing patients will end in April 2020, when the last patient enrolled by Hospira is due to complete the 3-year observation.

This will enable the Hospira and STADA patient data to be combined, resulting in a total sample size of at least 6206 patients and the combined data will be reported to the EMA in a joint clinical study report.

4,500 patients will be recruited by Hospira and the remainder will be the same epoetin zeta, conducted by STADA.

11. FINAL REPORT AND ARCHIVING

11.1. Final Report

A fully integrated report will be prepared. The final report will be signed by all responsible functions mentioned in the present observation protocol.

11.2. Archiving

The marketing authorisation holder shall make arrangements for archiving of all study related material for future access and/or evaluations for at least 10 years. Safety-related material will be kept by the marketing authorisation holder for an unlimited time.

12. CONFIDENTIALITY AND PUBLICATION OF RESULTS

All information concerning the present observation is strictly confidential.

Any publication requires the written consent of the sponsor.

13. LITERATURE

1. Blyth and Still: Binomial Confidence Intervals. Journal of the American Statistical Association, 78, 108 – 116.

2. Edwards IR, Biriell C. Harmonisation in pharmacovigilance. Drug Saf. 1994, 10(2) 93 – 102.

3. Kalbfleisch, JD., Prentice, RL. (1980): The Statistical Analysis of Failure Time Data. John Wiley and Sons. New York.

4. Lacombe C, Mayeux P. Erythropoietin (EPO) receptor and EPO mimetics. Adv Nephrol Necker Hosp. 1999, 29 177 – 189.

5. McKoy JM, Stonecash RE, Cournoyer D, Rossert J, Nissenson AR, Raisch DW, Casadevall N, Bennett CL. Epoetin-associated pure red cell aplasia: past, present, and future considerations. Transfusion 2008; 48:1754-1762.

6. Ridley DM, Dawkins F, Perlin E. Erythropoietin: a review. J Natl Med Assoc. 1994; 86(2):129 - 35.

7. Vollset, SE. (1993): Confidence Intervals for a Binomial Proportion. Statistics in Medicine 12, 809 - 824.

8. Wang GL, Semenza GL. Molecular basis of hypoxia-induced erythropoietin expression. Curr Opin Hematol. 1996, 3(2):156-62.

14. APPENDICES

Appendix 1. Protocol Amendment Change Letters (PACLs)

Protocol Administrative Change Letter (PACL)
C1111006/EPOE-09-11 (PASCO II)
FINAL 22 November 2016

Hospira UK Ltd, a Pfizer Company
Horizon, Honey Lane
Hurley, Maidenhead SL6 6RJ, UK

22 November 2016

Dear Investigator,

RE: Protocol Administrative Changes and Clarifications for Study C1111006 (EPOE-09-11)

Post-Authorisation Safety Cohort Observation

of Retacrit™ (epoetin zeta) Administered Subcutaneously

for the Treatment of Renal Anaemia (PASCO II)

This Protocol Administrative Change Letter (PACL) is to notify you of the following administrative changes to the PASCO II C1111006 (EPOE-09-11) protocol version 4, dated 20 March 2015.

This PACL makes the following administrative changes which are required to reflect the transition to Pfizer safety reporting processes and systems following the Pfizer acquisition of Hospira in 2015. These changes will be implemented from 09 December 2016.

1. **Change to Adverse Drug Reaction (ADR)/Adverse Event of Special Interest (AESI) Reporting Contact Details.**

The Hospira contact details used previously to notify all reportable safety events are changing. With effect from 09 December 2016 all safety events will be reported to the local Pfizer Drug Safety Unit (DSU) in your country. A list of current country-specific contact details for the DSUs is attached for reference (Attachment 1). These contact details can also be accessed at any time from the main page of the study EDC system.

This change relates to text in section 8.9.3 of the current version of the protocol.

2. **Change to ADR/AESI Report Forms**

The Hospira forms used to report ADRs, AESIs and other safety events are changing. With effect from 09 December 2016 all reportable safety events will be reported using the standard Pfizer Non-Interventional Study Adverse Event Form. A copy of the current Pfizer NIS Adverse Event Form is attached for reference (Attachment 2). This form can also be accessed at any time from the main page of the study EDC system.

This change relates to text in section 8.9.3 of the current version of the protocol.In the event that this protocol requires substantial changes in the future, the administrative changes described in this letter will be incorporated into the amended protocol.

Please inform your institutional review board/independent ethics committee of these changes, as required.

Yours sincerely,

Heather Fowler, PhD PMP
Clinical Operations Lead

cc: Trial Master File, Study Team

Protocol Administrative Change Letter (PACL)
C1111006/EPOE-09-11 (PASCO II)
FINAL, 16MAY2018

Hospira UK Ltd, a Pfizer Company
Horizon, Honey Lane
Hurley, Maidenhead SL6 6RJ, UK

16MAY2018

Dear Investigator,

RE: Protocol Administrative Changes and Clarifications for Study C1111006 (EPOE-09-11)

Post-Authorisation Safety Cohort Observation of Retacrit™ (epoetin zeta) Administered Subcutaneously for the Treatment of Renal Anaemia (PASCO II)

This Protocol Administrative Change Letter (PACL) is to notify you of the following administrative changes and/or clarifications to the PASCO II C1111006 (EPOE-09-11) protocol version 4.0, dated 20 March 2015.

1. Extension of maximum observation period for PASCOII.

The observation period for PASCOII is adjusted to reflect the extended period of study recruitment which was necessary to recruit the required number of patients for the study.

This study is a joint post-authorisation commitment of Stada and Hospira UK Ltd (a Pfizer company). Enrolment of the Hospira cohort of 4500 patients completed in April 2017; enrolment of the Stada cohort of 2200 patients is ongoing. The observation period details below have therefore also been adjusted to reflect these differential observation periods.

Observation period for PASCOII is amended from: max. 8 years to: max. 12 years. The overall time scheduled for the observation is thus amended:

Section 8.3 - TIME SCHEDULE: Old Wording (Protocol V4.0 dated 20MAR2015):

The overall time schedule for the observation is planned as follows:

- Start of Observation (Year): 2010
- Observation period per patient: up to 3 years

- Observation period PASCOII: max. 8 years
- End of Observation: 6700 patients completed the observation
- Final Report: end of observation + 6 months

Safety interim data will be compiled and reported in the framework of PSUR and RMP submissions. Annual progress reports are submitted to PRAC as per GVP Module VIII.

Section 8.3 TIME SCHEDULE: Revised Wording per PACL 16MAY2018:

- Start of Observation (Year): 2010
- Observation period per patient: up to 3 years
- Observation period PASCOII: max. 12 years
- End of Observation: 6700 patients completed the observation
- Final Report: end of observation + 6 months

2. Change of name for IPM laboratories to BioAgilytix Europe GmbH

The central laboratory for the evaluation of anti-drug antibodies has changed company name from IPM-GmbH to BioAgilytix Europe GmbH, following BioAgilytix acquisition of IPM-GmbH in 2016. The change of name became effective on 04JAN2018. Processes for laboratory sample shipments as well as laboratory assay protocols, remain unchanged.

The central laboratory address and contact details are therefore amended.

Section 8.8.1.1 PRIMARY ENDPOINTS: Old Wording (Protocol V4.0 dated 20MAR2015):

The central laboratory for the evaluation of antibodies will be:

IPM- GmbH, Lademannbogen 6122339 Hamburg, Germany

Phone: +49-40-53805-514 Fax:++49-40-53805-854

Section 8.8.1.1 PRIMARY ENDPOINTS: Revised Wording per PACL 16MAY2018:

The central laboratory for the evaluation of anti-drug antibodies will be:

BioAgilytix Europe GmbH, Lademannbogen 10, 22339 Hamburg, Germany

Phone: +49 (0) 40 526779 1 Email: pasco@bioagilytix.de

3. Clarification of 'Legal Representative' definition for Informed Consent.

Section 5.3 of the protocol states that "patients and /or their 'legal representatives' will be informed and asked for written informed consent regarding the collection and evaluation of data during the course of this non interventional study".

However, for this study the use of a 'legal representative' (an individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject to the subject's participation in the clinical trial) is restricted only to the consenting of minors. For adults, a 'legal representative' signature is not applicable. Section 5.3 has therefore been amended to clarify this.

Furthermore, where a patient is **physically unable** to provide written informed consent it is possible for a witness to sign and date the consent form on behalf of the study patient in the witness section provided, with a documented reason for doing so. Section 5.3 has therefore been amended to reflect this. Where applicable, informed consent documents with a section specifically for a witness signature will be approved prior to use by the relevant ethics committees.

Section 5.3 PATIENT INFORMATION/INFORMED CONSENT: Old Wording (Protocol V4.0 dated 20MAR2015):

Regarding the decision about therapy, there is no further information necessary which is beyond the physician's routine professional duty to inform the patient.

In this non-interventional study the physician is asked to provide, if available, remaining serum/plasma samples gained from routine laboratory determinations to a central specialized laboratory for the evaluation of the presence of anti-epoetin antibodies. In this case it is necessary to inform patients and/or their legal representatives of these potential additional laboratory tests and obtain written informed consent for the testing.

Participating patients and/or their legal representatives will be informed and asked for written informed consent regarding the collection and evaluation of data during the course of the non-interventional study.

The physician will ensure by written confirmation that informed consent was obtained and is available. The written confirmation and the informed consent will be archived by the physician.

Section 5.3 PATIENT INFORMATION/INFORMED CONSENT: Revised Wording per PACL 16MAY2018:

Regarding the decision about therapy, there is no further information necessary which is beyond the physician's routine professional duty to inform the patient.

In this non-interventional study the physician is asked to provide, if available, remaining serum/plasma samples gained from routine laboratory determinations to a central specialised laboratory for the evaluation of the presence of anti-epoetin antibodies. In this case it is necessary to inform patients (and their witness, where appropriate) or, in the case of minors, patients and their legal representatives of these potential additional laboratory tests and obtain written informed consent for the testing.

Participating patients (and their witness, where appropriate) or, in the case of minors, patients and their legal representatives will be informed and asked for written informed consent regarding the collection and evaluation of data during the course of the non-interventional study.

The physician will ensure by written confirmation that informed consent was obtained and is available. The written confirmation and the informed consent will be archived by the physician.

In the event that this protocol requires substantial changes in the future, the administrative changes described in this letter will be incorporated into the amended protocol.

Please inform your institutional review board/independent ethics committee of these changes, as required.

Yours sincerely,

Marcelo Garcia Da Rocha, MD

Global Medical Director, Clinical Development Biosimilars

cc: Trial Master File, Study Team

Protocol Administrative Change Letter
(PACL)
C1111006/EPOE-09-11 (PASCO II)
FINAL V1 0, 21NOV2018

Hospira UK Ltd, a Pfizer Company
Horizon, Honey Lane
Hurley, Maidenhead SL6 6RJ, UK

21NOV2018

Dear Investigator,

RE: Protocol Administrative Changes and Clarifications for Study C1111006 (EPOE-09-11)

Post-Authorisation Safety Cohort Observation

of Retacrit™ (epoetin zeta) Administered Subcutaneously

for the Treatment of Renal Anaemia (PASCO II)

This Protocol Administrative Change Letter (PACL) is to notify you of the following administrative changes to the PASCO II C1111006 (EPOE-09-11) protocol version 4.0, dated 20 March 2015.

1. **Transfer of Marketing Authorization (MA) Holder for PASCOII from Hospira UK Limited to Pfizer Europe MA European Economic Interest Grouping (EEIG).** The European Commission Decision for this transfer was adopted on 28SEP2018.

Cover Page: Old Wording (Protocol V4.0 dated 20MAR2015:

MARKETING AUTHORISATION HOLDER:
Hospira UK Limited
Queensway
Leamington Spa, UK
Tel: +44 1926 820820
Fax: +44 1926 834445

Address changing during 2015 to:
Hospira UK Limited
Horizon, Honey Lane
Hurley, Maidenhead SL6 6RJ, UK
Tel: +44 1628 515 500
Fax: +44 1628 824 776

Cover Page: Revised wording per PACL dated 21NOV2018:

Pfizer Europe MA EEIG

Boulevard de la Plaine 17

1050 Bruxelles

Belgium

Section 8.7.1 - Identity of Medication: Old Wording (Protocol V4.0 dated 20MAR2015):

Name of product:	Retacrit™
Active ingredient:	epoetin zeta
Mode of administration:	subcutaneous
Prescription status:	only available on prescription
Marketing authorisation holder:	Hospira UK Limited

For further information see current SmPC of Retacrit™.

Section 8.7.1 - Identity of Medication: Revised wording per PACL dated 21NOV2018:

Name of product:	Retacrit™
Active ingredient:	epoetin zeta
Mode of administration:	subcutaneous
Prescription status:	only available on prescription
Marketing authorisation holder:	Pfizer Europe MA EEIG

For further information see current SmPC of Retacrit™.

Section 4.0 LIST OF ABBREVIATIONS AND TERMS: Old Wording (Protocol V4.0 dated 20MAR2015)

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
CHMP	Committee for Medicinal Products for Human Use
cpm	Counts per minute
CRF	Case Report Form
CRO	Contract Research Organisation
EC	European Community
EDC	Electronic Data Capture
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agents
GVP	Good Pharmacovigilance Practice
HLT	High level term
MedDRA	Medical Dictionary for Regulatory Activities
PASCO	Post Authorisation Safety Cohort Observation
PRAC	Pharmacovigilance Risk Assessment Committee
PRCA	Pure red cell aplasia
PSUR	Periodic Safety Update Report
PT	Preferred term
RIP	Radio-immune-precipitation
rh-EPO	Recombinant human erythropoietin
RMP	Risk Management Plan
SC	subcutaneous
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard Operating Procedure
TC	Total amount of radioactive counts

Section 4.0 LIST OF ABBREVIATIONS AND TERMS: Revised Wording (per PACL

dated 21NOV2018)

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
CHMP	Committee for Medicinal Products for Human Use
cpm	Counts per minute
CRF	Case Report Form
CRO	Contract Research Organisation
EC	European Community
EDC	Electronic Data Capture
EEIG	European Economic Interest Grouping
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agents
GVP	Good Pharmacovigilance Practice
HLT	High level term
MA	Marketing Authorisation
MedDRA	Medical Dictionary for Regulatory Activities
PASCO	Post Authorisation Safety Cohort Observation

PRAC	Pharmacovigilance Risk Assessment Committee
PRCA	Pure red cell aplasia
PSUR	Periodic Safety Update Report
PT	Preferred term
RIP	Radio-immune-precipitation
rh-EPO	Recombinant human erythropoietin
RMP	Risk Management Plan
SC	subcutaneous
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard Operating Procedure
TC	Total amount of radioactive counts

In the event that this protocol requires substantial changes in the future, the administrative changes described in this letter will be incorporated into the amended protocol.

Please inform your institutional review board/independent ethics committee of these changes, as required.

Yours sincerely,

Marcelo Garcia Da Rocha, MD

Global Medical Director, Clinical Development Biosimilars

cc: Trial Master File, Study Team

Document Approval Record

Document Name:	C1111006 Protocol Amendment 4 (clean) 02 August 2019
Document Title:	C1111006 Protocol Amendment 4 (clean) 02 August 2019

Signed By:	Date(GMT)	Signing Capacity
Thiele, Alexandra	09-Aug-2019 19:33:59	Business Line Approver
De Bernardi, Barbara	13-Aug-2019 11:44:37	EUQPPV Approval